Original Article

Pathological evaluation of the visceral pleura in the radical pleurectomy/decortication for malignant pleural mesothelioma patients

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Background: Radical pleurectomy/decortication (P/D) is applied as a surgical treatment of resectable malignant pleural mesothelioma (MPM). Although P/D removed visceral pleura, dissection plain was not histologically explored previously. We examined a pathological evaluation of surgically removed visceral pleura in P/D.

Methods: Twenty-five patients with MPM who underwent P/D at the Tokyo Medical and Dental University Hospital between April 2010 and April 2018 were studied. The 25 cases included 20 with epithelioid tumors, 4 with a biphasic tumor and 1 with desmoplastic tumors. Nine, 1, 11 and 4 patients had mesotheliomas of stages I, II, III and IV, respectively. We analyzed the site of the visceral pleural lesions using the HE & Elastica van Gieson (EVG) staining. The tumor involvement of the pleura and the surgical dissection plane were defined using the depth criteria, D0–3. We added survival analyses according to the depth criteria.

Results: Ninety-nine lesions in total 45 lobes: 20 upper right, 14 middle, 20 lower, 22 upper left, and 23 lower were examined. Based on the depth D 0–3 criteria, there were 21 type D0, 18 type D1, 22 type D2 and 38 type D3 lesions. The growth of tumor cells in the pleura was partially diffuse or nodular in all cases. While 38 lesions which invaded the lung parenchyma were excised, another 61 lesions that reached within the pleura were dissected from lung parenchyma. Type D2&3 showed poor survivals than type D0&1.

Conclusions: The lung parenchyma was always the dissection plane in P/D, regardless of tumor involvement in the visceral pleura. The depth criteria would help us in classifying pleural invasion histologically and possibly predicting the prognosis.

Keywords: Radical pleurectomy/decortication (radical P/D); malignant pleural mesothelioma (MPM); macroscopic complete resection (MCR); visceral pleura; Elastica van Gieson stain (EVG stain)

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Introduction

In recent years, radical pleurectomy/decortication (P/D) for surgical treatment of patients with resectable malignant pleural mesothelioma (MPM) has been increasing (1,2). The outcomes of P/D are reported to be comparable to those of extrapleural pneumonectomy (EPP) with no significant difference in survival of patients with MPM (3-11). Macroscopic complete resection (MCR) in any surgical procedure for resectable MPM is critically important (12-14). While both P/D and EPP remove the parietal pleura similarly, P/D removes the visceral pleura with preserving the lung parenchyma. Visceral pleura is excised macroscopically by surgeons, and resected specimens are analyzed

Table 1 Clinical characteristics of patients

Case	Sex	Age, y	Operated side	Histology	pStage
1	Male	68	Right	Epithelioid	pT1bN0M0
2	Female	72	Left	Epithelioid	pT1bN0M0
3	Male	71	Left	Epithelioid	pT1bN0M0
4	Female	76	Left	Epithelioid	pT3N2M0
5	Male	55	Left	Epithelioid	pT3N0M0
6	Male	74	Right	Desmoplastic	pT2N0M0
7	Male	72	Right	Biphasic	pT2N2M0
8	Male	64	Right	Epithelioid	pT3N0M0
9	Male	59	Left	Epithelioid	pT3N0M0
10	Male	61	Right	Epithelioid	pT3N0M0
11	Male	65	Left	Epithelioid	pT1bN0M0
12	Male	66	Left	Biphasic	pT4N0M0
13	Male	57	Right	Epithelioid	pT4N2M0
14	Male	67	Left	Epithelioid	pT3N0M0
15	Male	69	Left	Epithelioid	pT1bN0M0
16	Male	73	Right	Epithelioid	pT2N0M0
17	Male	72	Left	Epithelioid	pT1aN0M0
18	Female	69	Left	Epithelioid	pT1bN0M0
19	Male	59	Left	Epithelioid	pT3N2M0
20	Male	70	Right	Biphasic	pT3N2M0
21	Male	76	Right	Epithelioid	pT3N0M0
22	Male	72	Left	Biphasic	pT3N2M0
23	Male	75	Right	Epithelioid	pT4N0M0
24	Male	64	Left	Epithelioid	ypT4N0M0
25	Male	63	Right	Epithelioid	pT2N0M0

histopathologically.

The visceral pleura consists of five-layers: mesothelial and medium subcutaneous layers, elastic plate, connective tissue and basement membrane (15). It is important to evaluate where in the five layers lies the actual dissection plane in P/D. There are no reports evaluating the pathology of the visceral pleura after P/D for patients with MPM. In this study, we examined a pathological assessment of surgically removed visceral pleura in P/D and added survival analyses according to the pathology.

Methods

Clinical characteristics of patients

Visceral pleura of consecutive 25 patients with MPM who received radical P/D under the setting of multimodality treatment consisting of surgery and postoperative chemotherapy at Tokyo Medical and Dental University Hospital between April 2010 and April 2018 were studied. The pathological stage was evaluated based on the IMIG staging system, and histological classification was based on the WHO classification (*Table 1*). Among these patients, there were 20 cases of epithelioid tumor, 1 of desmoplastic tumor and 4 of biphasic tumor. Nine patients had stage I MPM, one had stage II, 11 had stage III, and 4 had stage IV. Clinical records of all patients were fully documented.

This study was approved by the Ethics Committee of Tokyo Medical and Dental University (No. M2000-1097), and informed consent was obtained from all the patients.

Surgical procedure

All enrolled patients underwent P/D as their initial surgery. P/D was performed via a wide posterolateral thoracotomy through the sixth rib bed and additional incision at the ninth intercostal space. The parietal pleura was exfoliated radically, and the costal pleural layer was segregated from the endothoracic fascia. All the visceral pleura were removed by a blunt dissection to clear the tumors, leaving the lung parenchyma intact. The diaphragm or pericardium was resected and reconstructed, when the tumor invaded macroscopically. Finally, all patients received intraoperative intrapleural hyperthermic cisplatin perfusion for one hour (2). MCR was obtained in all patients.

Histologic evaluation of visceral pleura

In this study, only visceral pleural lesions were evaluated. Whole removed pleura including adjacent tissue after P/D was fixed in the formalin in the operating room. A few days later, both surgeons and pathologists identified the parietal and visceral pleura together in the pathology lab. At least two specimens of visceral pleura each lobe were obtained for histopathological analysis. We examined a total of 99 lesions in 45 lobes from 25 patients at the following sites: right upper lesions (n=20), middle lesions (n=14), lower lesions (n=20), left upper lesions (n=22), and lower lesions (n=23) (*Table 2*). Microscopic examinations were made from slides stained with both hematoxylin-eosin (H&E) and Elastica van Gieson (EVG) stains according to standard protocols. The decision to separate the pleura from the parenchyma was based on the macroscopic invasion of the disease. We defined the involvement of the visceral pleura using the depth criteria (*Figure 1*); type D0: no tumor involvement in the pleura; type D1: tumor involvement is not reaching the elastic plate; type D2: tumor involvement between the elastic plate and the basement membrane and type D3: tumor involvement up to the lung parenchyma. The structures of mesothelial and medium subcutaneous layers, elastic plate, connective tissue, basement membrane, lung parenchyma, and the separation of the pleural surfaces were pathologically evaluated by H&E and EVG staining of the pleura in 99 lesions collected from 25 patients. The stained sections were examined by two authors (M Kobayashi and C Takasaki) without knowledge of the patient characteristics.

Table 2 Evaluation of dissection of the visceral pleura site

Site	Upper	Middle	Lower	Total
Right	20	14	20	54
Left	22	–	23	45
Total	42	14	43	99

Statistical analysis

We analyzed overall survival (OS) and disease recurrence-free survival (DFS) of patients and compared 2 groups with or without invasion to elastic layer in the visceral pleura. We defined D0&1 as without invasion to elastic layer and D2&3 as with invasion. When different depth criteria were

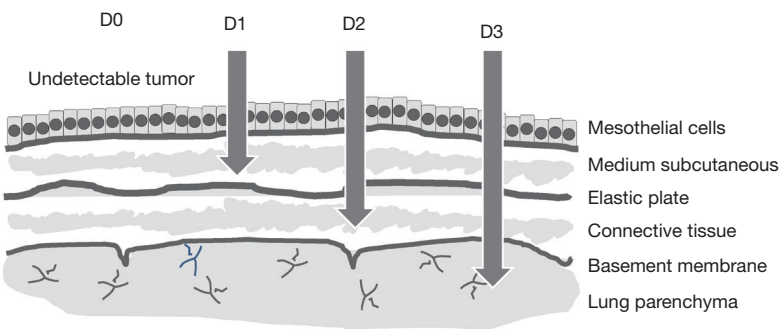

Figure 1 Criteria for the evaluation of the visceral pleura site. D0: no tumor involvement in the pleura; D1: tumor involvement no reaching the elastic plate layer; D2: tumor involvement between elastic layer and basement membrane; D3: tumor involvement to the lung parenchyma.

seen in different lobes in a patient, the deepest one was applied. OS was considered as the period from primary surgery to death of the patient or last contact. DFS was considered as the period from primary surgery to diagnosis of first recurrence or last contact. OS and DFS were estimated using the product-limit procedure (Kaplan-Meier method). P<0.05 was considered statistically significant. All statistical analyses were performed using Stat View version 5.0 (SAS Institute Inc.).

Results

Pathological evaluation

In all the evaluated specimens, the growth of tumor cells on the visceral pleural surface showed either a partially diffuse or nodular pattern. Based on the depth criteria, the lesions were grouped as follows: 21 of type D0 (*Figure 2A*,*B*), 14 of type D1 (*Figure 2C*,*D*), 22 of type D2 (*Figure 2E*,*F*) and 38 of type D3 (*Figure 2G*,*H*) (*Table 3*). Using both HE and EVG staining, histopathological analyses revealed that the dissection plane was the lung parenchyma in all specimens, regardless of tumor involvement. Additionally, the dissection plane of type D3 was deeper in the lung parenchyma compared to that of types D0–2. Therefore, our findings demonstrate that in cases of MPM undergoing P/D, the visceral pleura dissection plane is the lung parenchyma.

Survivals analysis

OS in type D0&1 and type D2&3 were shown in *Figure 3*. DFS in type D0&1 and type D2&3 were shown in *Figure 4*. Type D0&1 was associated with better OS (P=0.018) and DFS (P=0.024) than type D2&3.

Discussion

It is difficult to evaluate the involvement of the visceral pleura at preoperative. Pinelli *et al.* assessed the involvement of the visceral pleura by studying the endoscopic patterns of plural invasion in patients with MPM (16). They showed that the cytology of the pleural fluid and the endoscopic appearance were associated with the detection of an advanced stage MPM. It is clear that the prognosis of MPM is related to the extent of visceral pleura involvement independent of parietal pleura involvement (17-19). However, endoscopic examination does not always reveal the extent of visceral pleura invasion. The depth of pleural invasion can be defined only by histopathological investigation.

The essence of P/D is to preserve the lung parenchyma, and it is critical to perform an accurate dissection of the pleural lesions. However, there is no report that evaluates the location of the visceral pleura dissection plane. We established the depth type criteria, to determine the dissection plane in P/D. We scored the tumor involvement based on HE and EVG staining. While the HE staining detects MPM cells in the visceral pleura, the EVG staining evaluates the elastic plate and the basement membrane. A combination of these staining methods helped demonstrate the depth of tumor invasion and dissection plane of the visceral pleurectomy, accurately.

The five-layer structure of the pleura is arranged in the order of mesothelial layer, sub mesothelial layer, elastic plate, connective tissue, and basement membrane (15). MPM cells in the pleural surface extend from the mesothelial layer deep into the lung parenchyma. We evaluated the visceral pleura side in the resected MPMs using the depth criteria. Tumor involvement based on depth was categorized into types D0–3 (*Figure 1*). As a result, we have shown that the visceral pleura dissection plane was the lung parenchyma regardless of tumor depth. Dissection of the visceral pleura between the tumor and normal was achieved by blunt dissection. Analyses of these findings show that types D0/D1, and D2 has no tumor involvement in the lung parenchyma with some thickening of the mesothelial layer. On the other hand, type D3 was found to have thicker pleura compared to types D0–2, and dissection of the tumor involved going deeper into the lung parenchyma. Therefore, regardless of the tumor, the dissection plane was always within the lung parenchyma.

Decortication of the lung in chronic pleural empyema is performed as a surgical treatment (20-23). Chronic pleural empyema is caused by tuberculosis or other bacterial infection (22). Previous reports have described the dissection plane on the visceral pleura side and reasoned that the visceral pleura remains normal, between the “peel” and the visceral pleura behind the basement membrane (20,23). Pleural thickening occurred with the inflammatory process of dense collagenous fibrous tissue around the pleural mesothelium layer in chronic empyema. On the other hand, pleural thickening in MPM is affected by tumor growth. MPM cells proliferate in visceral pleura, however, dissection plane does not occur within the visceral pleura structure. Malignant disease is potentially different from benign

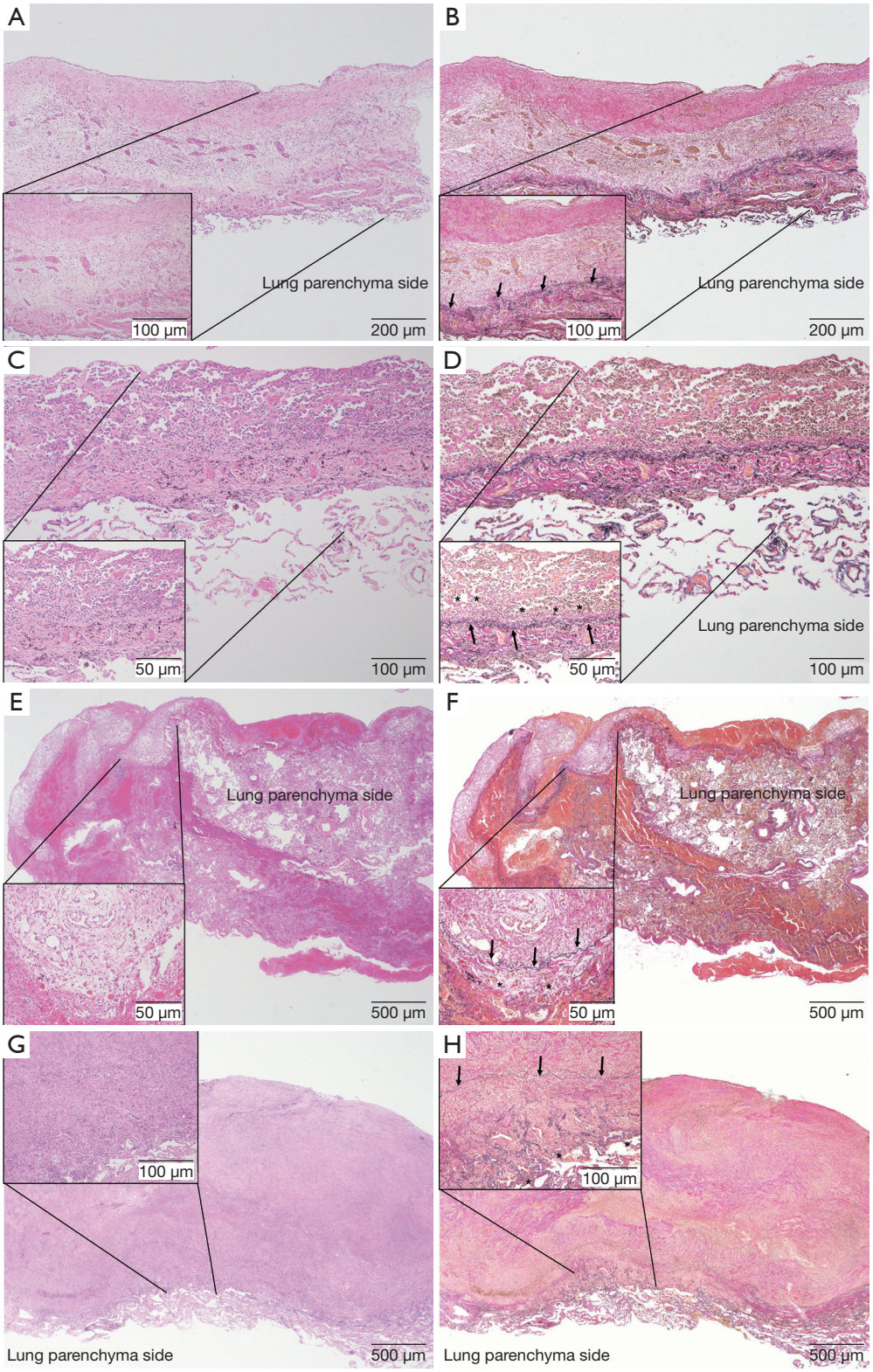

Figure 2 Criteria for the evaluation of the visceral pleura site. (A) Type D0 (HE); (B) type D0 (EVG); (C) type D1 (HE); (D) type D1 (EVG); (E) type D2 (HE); (F) type D2 (EVG); (G) type D3 (HE); (H) type D3 (EVG), all lesions were defined by depth type criteria. Black arrow: elastic plate layer, *: front of tumor invasion site.

Table 3 Tumor involvement defined in depth criteria

Type	D0	D1	D2	D3
Number	21	18	22	38

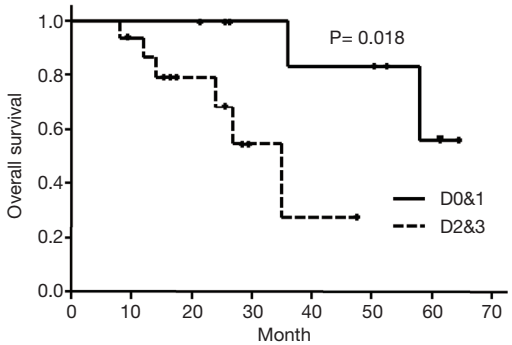

Figure 3 Comparison of overall survival curve between type D0&1 and type D2&3. The overall survival was significantly lower in patients with type D2&3 than in those with type D0&1.

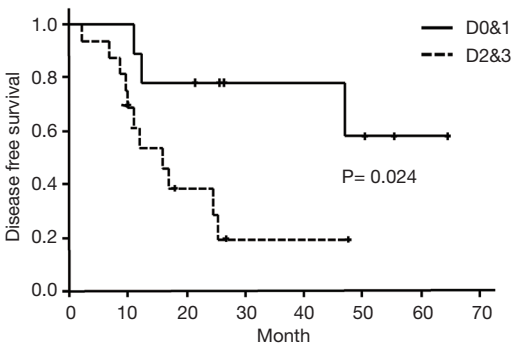

Figure 4 Comparison of disease recurrence-free survival curve between type D0&1 and type D2&3. The disease recurrence-free survival was significantly lower in patients with type D2&3 than in those with type D0&1.

inflammatory diseases

In addition to pathological assessment of visceral pleura, we analyzed the relationship between depth of the tumor invasion and prognosis. Tumor involvement into elastic plate influenced poor prognosis and high recurrence rate. The depth criteria of visceral pleura could help us in classifying pleural invasion histologically and possibly predicting the prognosis.

This study has several limitations. First, it had a small number of cases from a single institution. Future collaborative research using larger sample sizes to obtain an agreement of dissection plane of the procedure. Second, not all of the visceral pleura were microscopically examined in the MPM patients. Third, being a retrospective study, a patient bias could have existed.

Conclusions

In P/D for MPM, the dissection plane of visceral pleura was the lung parenchyma regardless of tumor involvement. Pathological assessment with the depth criteria of pleural invasion would provide a classification of pleural involvement and an estimate of the prognosis.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Ethics Committee of Tokyo Medical and Dental University (No. M2000-1097), and informed consent was obtained from all the patients.

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